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☐ 6. Document ID: US 5891696 A

L2: Entry 6 of 8 File: USPT Apr 6, 1999

US-PAT-NO: 5891696
DOCUMENT-IDENTIFIER: US 5891696 A

TITLE: Compositions for cytochrome P450 biotransformation reactions

DATE-ISSUED: April 6, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Shaw; Peter M.	Madison	WI		
Lowery; Robert G.	Brooklyn	WI		
Thompson; David V.	Monona	WI		

US-CL-CURRENT: 435/189

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 7. Document ID: US 5786344 A

L2: Entry 7 of 8 File: USPT Jul 28, 1998

US-PAT-NO: 5786344
DOCUMENT-IDENTIFIER: US 5786344 A

TITLE: Camptothecin drug combinations and methods with reduced side effects

DATE-ISSUED: July 28, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ratain; Mark J.	Chicago	IL		
Gupta; Elora	Chicago	IL		

US-CL-CURRENT: 514/100; 424/143.1, 514/171, 514/183, 514/211.07, 514/211.08, 514/28, 514/9

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 8. Document ID: WO 200006776 A1 AU 9952256 A EP 1100968 A1

L2: Entry 8 of 8 File: DWPI Feb 10, 2000

DERWENT-ACC-NO: 2000-195321
DERWENT-WEEK: 200017

TITLE: Novel human UDP-glucuronosyltransferase sequence, polymorphisms for genotyping individuals to predict rate of metabolism of substrates and for identifying potential drug interactions

INVENTOR: GALVIN, M; MILLER, A ; PENNY, L ; RIEDY, M

PATENT-ASSIGNEE:

ASSIGNEE	CODE
AXYS PHARM INC	AXYSN

PRIORITY-DATA: 1998US-094391P (July 28, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200006776 A1	February 10, 2000	E	072	C12Q001/68
AU 9952256 A	February 21, 2000		000	C12Q001/68
EP 1100968 A1	May 23, 2001	E	000	C12Q001/68

DESIGNATED-STATES: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 200006776A1	July 22, 1999	1999WO-US16675	
AU 9952256A	July 22, 1999	1999AU-0052256	
AU 9952256A		WO 200006776	Based on
EP 1100968A1	July 22, 1999	1999EP-0937416	
EP 1100968A1	July 22, 1999	1999WO-US16675	
EP 1100968A1		WO 200006776	Based on

INT-CL (IPC): C12 Q 1/68

ABSTRACTED-PUB-NO: WO 200006776A
BASIC-ABSTRACT:

NOVELTY - New isolated non-chromosomal nucleic acid molecules (I) of 57 sequences, all fully defined in the specification, comprising human UDP-glucuronosyltransferase (UGT2B) sequence polymorphism, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a nucleic acid probe (P) for detecting UGT2B locus polymorphism comprising (I);

(2) an array oligonucleotides comprising 2 or more (P); and

(3) a method for detecting a polymorphism in a UGT2B metabolism of a substrate, in an individual, comprising analyzing the genome of the individual for the presence of (I),

which indicates an alteration of the UGT2B expression or activity.

USE - (P) is used for detecting polymorphism in an individual (claimed). (I) is used in screening assays and for genotyping individuals, used to predict their rate of metabolism of UGT2B substrates, potential drug-drug interactions and adverse side effects. The polymorphisms can be used as single nucleotide polymorphism for detecting genetic linkage related to phenotypic variation in activity or expression of UGT2B protein. (I) is also used for generating genetically modified non-human animals and for obtaining site specific gene modification in cell lines.

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: NOVEL HUMAN SEQUENCE POLYMORPH INDIVIDUAL PREDICT RATE METABOLISM SUBSTRATE IDENTIFY POTENTIAL DRUG INTERACT

DERWENT-CLASS: B04 D16

CPI-CODES: B04-E02E; B04-E05; B11-C08E4; B12-K04A3; D05-H09; D05-H12B1; D05-H12D1; D05-H18A;

CHEMICAL-CODES:

Chemical Indexing M1 *01*
Fragmentation Code
M423 M710 M750 M781 M905 N102 P831 Q233 Q505
Specfic Compounds
A00NSA A00NSD A00NSN

Chemical Indexing M6 *02*
Fragmentation Code
M905 P831 Q233 Q505 R515 R521 R627 R639

SECONDARY-ACC-NO:
CPI Secondary Accession Numbers: C2000-060611

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Term	Documents
UDP.DWPI,USPT.	2695
UDPS.DWPI,USPT.	14
GLUCURONOSYLTRANSFERASE.DWPI,USPT.	59
GLUCURONOSYLTRANSFERASES.DWPI,USPT.	23
POLYMORPHIS$	0
POLYMORPHIS.DWPI,USPT.	12
POLYMORPHISEME.DWPI,USPT.	2
POLYMORPHISH.DWPI,USPT.	1
POLYMORPHISIM.DWPI,USPT.	15
POLYMORPHISIMS.DWPI,USPT.	7
(UDP GLUCURONOSYLTRANSFERASE AND POLYMORPHIS$).USPT,DWPI.	8

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L4 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:107902 CAPLUS
DOCUMENT NUMBER: 136:161325
TITLE: Flavopiridol drug combinations with glucuronosyltransferase activity enhancer and methods with reduced side effects by enhancing its metabolism
INVENTOR(S): Ratain, Mark J.; Innocenti, Federico; Iyer, Lalitha
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 64 pp., Cont.-in-part of U.S. Ser. No. 553,829.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002016293	A1	20020207	US 2001-835082	20010412

PRIORITY APPLN. INFO.: US 2000-553829 A2 20000421
AB This invention provides methods, formulations and kits to reduce the toxicity of flavopiridol and analogs thereof. Disclosed are therapeutics and treatment methods employing such drugs in combination with agents that increase conjugative enzyme activity or glucuronosyltransferase activity, and agents that decrease biliary transport protein activity, such as cyclosporine A, the resultant effects of which are to decrease the significant side effects previously assocd. with treatment using these drugs. The invention also characterizes specific isoforms of glucuronyltransferase enzymes involved in glucuronidation of flavopiridols and their analogs.

L4 ANSWER 2 OF 8 MEDLINE
ACCESSION NUMBER: 2002424756 IN-PROCESS
DOCUMENT NUMBER: 22169263 PubMed ID: 12181437
TITLE: Common Human UGT1A **Polymorphisms** and the Altered Metabolism of Irinotecan Active Metabolite 7-Ethyl-10-hydroxycamptothecin (SN-38).
AUTHOR: Gagne Jean-Francois; Montminy Valerie; Belanger Patrick; Journault Kim; Gaucher Genevieve; Guillemette Chantal
CORPORATE SOURCE: Faculty of Pharmacy, Laval University, Quebec, Canada.
SOURCE: MOLECULAR PHARMACOLOGY, (2002 Sep) 62 (3) 608-17.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020816
Last Updated on STN: 20020816
AB 7-Ethyl-10-hydroxycamptothecin (SN-38) is the pharmacologically active metabolite of irinotecan, in addition to being responsible for severe toxicity. Glucuronidation is the main metabolic pathway of SN-38 and has been shown to protect against irinotecan-induced gastrointestinal toxicity. The purpose of this study was to determine whether common polymorphic UDP-glucuronosyltransferase (UGT) affects SN-38 glucuronidation. First, kinetic characterization of SN-38-glucuronide (SN-38-G) formation was assessed for all known human UGT1A and UGT2B overexpressed in human embryonic kidney 293 cells. To assess the relative

activity of UGT isoenzymes for SN-38, rates of formation of SN-38-G were monitored by liquid chromatography/mass spectrometry analysis and normalized by level of UGT cellular expression. Determination of intrinsic clearances predicts that hepatic UGT1A1 and **UGT1A9** and the extrahepatic UGT1A7 are major components in SN-38-G formation, whereas a minor role is suggested for UGT1A6, UGT1A8, and UGT1A10. In support of the involvement of **UGT1A9**, a strong coefficient of correlation was observed in the glucuronidation of SN-38 and a substrate, mainly glucuronidate, by **UGT1A9** (flavopiridol) by human liver microsomes (coefficient of correlation, 0.905; p = 0.002). In vitro functional experiments revealed a negative impact of the UGT1A1 allelic variants. Residual activities of 49, 7, 8, and 11% were observed for UGT1A1*6 (G(71)R), UGT1A1*27 (P(229)Q), UGT1A1*35 (L(233)R), and UGT1A1*7 (Y(486)D), respectively. Common variants of UGT1A7, UGT1A7*3 (N(129)K;R(131)K;W(208)R), and UGT1A7*4 (W(208)R), displayed residual activities of 41 and 28% compared with the UGT1A7*1 allele. Taken together, these data provide the evidence that molecular determinants of irinotecan response may include the UGT1A **polymorphisms** studied herein and common genetic variants of the hepatic **UGT1A9** isoenzyme yet to be described.

L4 ANSWER 3 OF 8 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001642489 MEDLINE
DOCUMENT NUMBER: 21534497 PubMed ID: 11677206
TITLE: Genetic link of hepatocellular carcinoma with **polymorphisms** of the UDP-glucuronosyltransferase UGT1A7 gene.
AUTHOR: Vogel A; Kneip S; Barut A; Ehmer U; Tukey R H; Manns M P; Strassburg C P
CORPORATE SOURCE: Department of Gastroenterology and Hepatology, Hannover Medical School, Hannover, Germany.
CONTRACT NUMBER: CA79834 (NCI)
SOURCE: GASTROENTEROLOGY, (2001 Nov) 121 (5) 1136-44. Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011107
Last Updated on STN: 20020122
Entered Medline: 20011205

AB BACKGROUND & AIMS: Hepatocellular carcinoma is associated with risk factors including hepatitis C, hepatitis B, cirrhosis, genetic liver diseases, and environmental carcinogens. Uridine 5'-diphosphate-glucuronosyltransferases are a superfamily of detoxifying enzymes capable of tobacco-borne carcinogen detoxification and cellular protection. This study examines the association of UGT1A7 and **UGT1A9** gene **polymorphisms** with hepatocellular carcinoma. METHODS: Genomic DNA from the blood of 59 patients with hepatocellular carcinoma and 70 control subjects without evidence of cancer was analyzed by UGT1A7- and **UGT1A9**-specific PCR, sequencing analysis, and temperature gradient gel electrophoresis. RESULTS: Three UGT1A7 missense mutations were detected defining the UGT1A7*2, UGT1A7*3, and UGT1A7*4 alleles. Wild-type UGT1A7 alleles were present in 41.4% of controls but only in 6.8% of cancer patients (P < 0.001; odds ratio [OR], 9.73; 95% confidence interval

[CI], 3.17-29.83). UGT1A7 **polymorphisms** were present in 93.2% of hepatocellular cancer patients, 74.5% carried the UGT1A7*3 allele (P < 0.001; OR, 10.76; 95% CI, 4.75-24.38), which combines the W208R, N129K, and R131K mutations and encodes a protein with low carcinogen detoxification activity. No **UGT1A9 polymorphisms** were detected. CONCLUSIONS: The significant association of hepatocellular carcinoma with the UGT1A7*3 allele encoding a low detoxification activity protein is identified and implicates UGT1A7 as a risk gene of hepatocarcinogenesis in addition to a role as potential marker for cancer risk assessment in chronic liver disease.

L4 ANSWER 4 OF 8 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001379554 EMBASE
TITLE: Human liver UDP-glucuronosyltransferase isoforms involved in the glucuronidation of 7-ethyl-10-hydroxycamptothecin.
AUTHOR: Hanioka N.; Ozawa S.; Jinno H.; Ando M.; Saito Y.; Sawada J.
CORPORATE SOURCE: N. Hanioka, Division of Environmental Chemistry, Natl. Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku,
Tokyo 158-8501, Japan. hanioka@nihs.go.jp
SOURCE: Xenobiotica, (2001) 31/10 (687-699).
Refs: 43
ISSN: 0049-8254 CODEN: XENOBH
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB 1. The human liver UDP-glucuronosyltransferase (UGT) isoforms involved in the glucuronidation of 7-ethyl-10-hydroxycamptothecin (SN-38), the active metabolite of irinotecan (CPT-11), have been studied using microsomes from human liver and insect cells expressing human UGTs (1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B15). 2. The glucuronidation of SN-38 was catalysed by UGT1A1, UGT1A3, UGT1A6 and **UGT1A9** as well as by liver microsomes. Among these UGT isoforms, UGT1A1 showed the highest activity of SN-38 glucuronidation at both low (1 .mu.M) and high (200 .mu.M) substrate concentrations. The ranking in order of activity at low and high substrate concentrations was UGT1A1 > **UGT1A9** > UGT1A6 > UGT1A3 and UGT1A1 > UGT1A3 > UGT1A6 .gtoreq. **UGT1A9**, respectively. 3. The enzyme kinetics of SN-38 glucuronidation were examined by means of Lineweaver-Burk analysis. The activity of the glucuronidation in liver microsomes exhibits a monophasic kinetic pattern, with an apparent K(m) and V(max) of 35.9 .mu.M and 134 pmol min(-1) mg(-1) protein, respectively. The UGT isoforms involved in SN-38 glucuronidation could be classified into two types: low-K(m) types such as UGT1A1 and **UGT1A9**, and high-K(m) types such as UGT1A3 and UGT1A6, in terms of affinity toward substrate. UGT1A1 had the highest V(max) followed by UGT1A3. V(max) of UGT1A6 and **UGT1A9** were approximately 1/9 to 1/12 of that of UGT1A1. 4. The activity of SN-38 glucuronidation by liver microsomes and UGT1A1 was effectively inhibited by bilirubin. Planar and bulky phenols substantially inhibited the SN-38 glucuronidation activity of liver microsomes and **UGT1A9**, and/or UGT1A6. Although cholic acid derivatives strongly inhibited the activity of SN-38 glucuronidation by UGT1A3, the inhibition profile did not parallel that in liver microsomes. 5. These results demonstrate that at least four UGT1A isoforms

are responsible for SN-38 glucuronidation in human livers, and suggest that the role and contribution of each differ substantially.

L4 ANSWER 5 OF 8 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001287826 MEDLINE
DOCUMENT NUMBER: 21199489 PubMed ID: 11302935
TITLE: Epirubicin glucuronidation is catalyzed by human UDP-glucuronosyltransferase 2B7.
AUTHOR: Innocenti F; Iyer L; Ramirez J; Green M D; Ratain M J
CORPORATE SOURCE: The University of Chicago, Department of Medicine, Chicago, IL 60637, USA.
CONTRACT NUMBER: GM61393 (NIGMS)
SOURCE: DRUG METABOLISM AND DISPOSITION, (2001 May) 29 (5) 686-92. Journal code: 9421550. ISSN: 0090-9556.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered Medline: 20010614

AB Epirubicin is one of the most active agents for breast cancer. The formation of epirubicin glucuronide by liver UDP-glucuronosyltransferase (UGT) is its main inactivating pathway. This study aimed to investigate epirubicin glucuronidation in human liver microsomes, to identify the specific UGT isoform for this reaction, and to correlate epirubicin glucuronidation with other UGT substrates. Microsomes from human livers were used. UGTs specifically expressed in cellular systems, as well as two UGT2B7 variants, were screened for epirubicin glucuronidation. Epirubicin, morphine, and SN-38 glucuronides were measured by high-pressure liquid chromatography. The mean +/- S.D. formation rate of epirubicin glucuronide in human liver microsomes (n = 47) was 138 +/- 37 pmol/min/mg (coefficient of variation, 24%). This phenotype was normally distributed. We screened commercially available UGT1A1, UGT1A3, UGT1A4, UGT1A6, **UGT1A9**, UGT2B7, and UGT2B15 for epirubicin glucuronidation. Only UGT2B7 converted epirubicin to its glucuronide. No differences in epirubicin glucuronidation were found in HK293 cells expressing the two UGT2B7 variants at position 268. Catalytic efficiency (V(max)/K(m)) of epirubicin glucuronidation was 1.4 microl/min/mg, a value higher than that observed for morphine, a substrate of UGT2B7. Formation of epirubicin glucuronide was significantly related to that of morphine-3-glucuronide ($r = 0.76$, $p < 0.001$) and morphine-6-glucuronide ($r = 0.73$, $p < 0.001$). No correlation was found with SN-38, a substrate of UGT1A1 ($r = 0.04$). UGT2B7 is the major human UGT catalyzing epirubicin glucuronidation, and UGT2B7 is the candidate gene for this phenotype. The reported tyrosine to histidine **polymorphism** in UGT2B7 does not alter the formation rate of epirubicin glucuronide, and undiscovered genetic **polymorphisms** in UGT2B7 might change the metabolic fate of this important anticancer agent.

L4 ANSWER 6 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:529964 BIOSIS

DOCUMENT NUMBER: PREV200100529964
TITLE: Genetic link of hepatocellular carcinoma with **polymorphisms** of the UDP-glucuronosyltransferase UGT1A7 gene.
AUTHOR(S): Vogel, Arndt (1); Kneip, Susanne (1); Barut, Ayse (1); Ehmer, Ursula (1); Tukey, Robert H.; Manns, Michael P.; Strassburg, Christian P.
CORPORATE SOURCE: (1) Hannover Medical School, Hannover Germany
SOURCE: Hepatology, (October, 2001) Vol. 34, No. 4 Pt. 2, pp. 176A.
print.
Meeting Info.: 52nd Annual Meeting and Postgraduate Courses
of the American Association for the Study of Liver Diseases
Dallas, Texas, USA November 09-13, 2001
ISSN: 0270-9139.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L4 ANSWER 7 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:380300 BIOSIS
DOCUMENT NUMBER: PREV200100380300
TITLE: Pharmacogenetics of UDP-glucuronosyltransferases: Significance in cancer chemotherapy.
AUTHOR(S): Iyer, L. (1)
CORPORATE SOURCE: (1) University of Chicago, Chicago, IL USA
SOURCE: Clinical Chemistry, (June, 2001) Vol. 47, No. S6, pp. S15.
print.
Meeting Info.: 53rd Annual Meeting of the AACC/CSCC
Chicago, Illinois, USA July 29-August 02, 2001
ISSN: 0009-9147.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L4 ANSWER 8 OF 8 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999168817 EMBASE
TITLE: Functions and transcriptional regulation of PAH-inducible human UDP- glucuronosyl-transferases.
AUTHOR: Bock K.W.; Gschaidmeier H.; Heel H.; Lehmkoster T.; Munzel P.A.; Bock-Hennig B.S.
CORPORATE SOURCE: K.W. Bock, Institute of Toxicology, University of Tubingen,
Wilhelmstrasse 56, D-72074 Tubingen, Germany
SOURCE: Drug Metabolism Reviews, (1999) 31/2 (411-422).
Refs: 44
ISSN: 0360-2532 CODEN: DMTRAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Functions and regulation of selected human UDP-glucuronosyltransferases (UGT1A1, UGT1A4, UGT1A6, **UGT1A9**, UGT2B7, UGT2B15) are summarized. Evidence for at least two PAH-inducible UGTs (UGT1A6 and **UGT1A9**) is presented, which, however, are also constitutively expressed in a tissue- and cell-specific manner. These isoforms have

recently been characterized to conjugate planar and bulky phenols, respectively. Using a selective RT-PCR method, UGT1A6 expression was detected in a variety of tissues (liver, kidney, lung, intestine, and pharyngeal mucosa). PAH-inducible UGTs may cooperate in the metabolism of phenolic metabolites of benzo(a)pyrene. Studies with stably expressed isoforms suggest that UGTIA9 is responsible for the formation of benzo(a)pyrene-3.6-diphenol diglucuronide, the major biliary metabolite of benzo(a)pyrene.

22169263 PubMed ID: 12181437
TITLE: Common Human UGT1A **Polymorphisms** and the Altered Metabolism of Irinotecan Active Metabolite 7-Ethyl-10-hydroxycamptothecin (SN-38).
AUTHOR: Gagne Jean-Francois; Montminy Valerie; Belanger Patrick; Journault Kim; Gaucher Genevieve; Guillemette Chantal
CORPORATE SOURCE: Faculty of Pharmacy, Laval University, Quebec, Canada.
SOURCE: MOLECULAR PHARMACOLOGY, (2002 Sep) 62 (3) 608-17. Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020816
Last Updated on STN: 20020816

AB 7-Ethyl-10-hydroxycamptothecin (SN-38) is the pharmacologically active metabolite of irinotecan, in addition to being responsible for severe toxicity. Glucuronidation is the main metabolic pathway of SN-38 and has been shown to protect against irinotecan-induced gastrointestinal toxicity. The purpose of this study was to determine whether common polymorphic UDP-glucuronosyltransferase (UGT) affects SN-38 glucuronidation. First, kinetic characterization of SN-38-glucuronide (SN-38-G) formation was assessed for all known human UGT1A and UGT2B overexpressed in human embryonic kidney 293 cells. To assess the relative activity of UGT isoenzymes for SN-38, rates of formation of SN-38-G were monitored by liquid chromatography/mass spectrometry analysis and normalized by level of UGT cellular expression. Determination of intrinsic clearances predicts that hepatic UGT1A1 and **UGT1A9** and the extrahepatic UGT1A7 are major components in SN-38-G formation, whereas a minor role is suggested for UGT1A6, UGT1A8, and UGT1A10. In support of the involvement of **UGT1A9**, a strong coefficient of correlation was observed in the glucuronidation of SN-38 and a substrate, mainly glucuronidate, by **UGT1A9** (**flavopiridol**) by human liver microsomes (coefficient of correlation, 0.905; p = 0.002). In vitro functional experiments revealed a negative impact of the UGT1A1 allelic variants. Residual activities of 49, 7, 8, and 11% were observed for UGT1A1*6 (G(71)R), UGT1A1*27 (P(229)Q), UGT1A1*35 (L(233)R), and UGT1A1*7 (Y(486)D), respectively. Common variants of UGT1A7, UGT1A7*3 (N(129)K;R(131)K;W(208)R), and UGT1A7*4 (W(208)R), displayed residual activities of 41 and 28% compared with the UGT1A7*1 allele. Taken together, these data provide the evidence that molecular determinants of irinotecan response may include the UGT1A **polymorphisms** studied herein and common genetic variants of the hepatic **UGT1A9** isoenzyme yet to be described.

L3 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:380300 BIOSIS
DOCUMENT NUMBER: PREV200100380300
TITLE: Pharmacogenetics of UDP-glucuronosyltransferases: Significance in cancer chemotherapy.
AUTHOR(S): Iyer, L. (1)
CORPORATE SOURCE: (1) University of Chicago, Chicago, IL USA
SOURCE: Clinical Chemistry, (June, 2001) Vol. 47, No. S6, pp. S15. print.
Meeting Info.: 53rd Annual Meeting of the AACC/CSCC Chicago, Illinois, USA July 29-August 02, 2001
ISSN: 0009-9147.
DOCUMENT TYPE: Conference

LANGUAGE: English
SUMMARY LANGUAGE: English

L3 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:107902 CAPLUS
DOCUMENT NUMBER: 136:161325
TITLE: **Flavopiridol** drug combinations with glucuronosyltransferase activity enhancer and methods with reduced side effects by enhancing its metabolism
INVENTOR(S): Ratain, Mark J.; Innocenti, Federico; Iyer, Lalitha
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 64 pp., Cont.-in-part of U.S. Ser. No. 553,829.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002016293	A1	20020207	US 2001-835082	20010412
PRIORITY APPLN. INFO.:			US 2000-553829 A2	20000421

AB This invention provides methods, formulations and kits to reduce the toxicity of **flavopiridol** and analogs thereof. Disclosed are therapeutics and treatment methods employing such drugs in combination with agents that increase conjugative enzyme activity or glucuronosyltransferase activity, and agents that decrease biliary transport protein activity, such as cyclosporine A, the resultant effects of which are to decrease the significant side effects previously assocd. with treatment using these drugs. The invention also characterizes specific isoforms of glucuronyltransferase enzymes involved in glucuronidation of flavopiridols and their analogs.

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